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EDITORIAL

Frank Bloos
Zhongheng Zhang
Thierry Boulain

Lactate-guided resuscitation saves lives: yes

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F. Bloos (✉)
Department of Anesthesiology and Intensive Care Medicine, Jena University Hospital, 07740 Jena, Germany
e-mail: frank.bloos@med.uni-jena.de
Tel.: +49-3641-9323283

F. Bloos
Center for Sepsis Control and Care, Jena University Hospital, Jena, Germany

Z. Zhang
Department of Critical Care Medicine, Jinhua Municipal Central Hospital, Jinhua Hospital of Zhejiang University, Zhejiang, People's Republic of China

T. Boulain
Medical-Surgical Intensive Care Unit, Centre Hospitalier Régional d'Orléans, Orléans, France

Introduction

Shock is defined as a mismatch between tissue O_2 needs and O_2 delivery. Arterial hypotension is frequently present in patients with shock but may occur late and not all types of shock are associated with arterial hypotension. While blood pressure is easy to measure, true assessment of the adequacy of tissue oxygenation is a challenge. There is an ongoing debate whether the measurement of serum lactate concentration can guide the physician in the diagnosis of shock and use of resuscitation strategies.

Lactate formation in shock: the entangled hypoxic and glycolytic pathways

During glycolysis, a succession of cytosolic enzymatic reactions, which do not need O_2, convert glucose to pyruvate. Pyruvate is either transported into the mitochondria and converted to acetyl-CoA by pyruvate dehydrogenase (PDH) to enter the tricarboxylic acid cycle that, together with O_2, fuels the synthesis of adenosine triphosphate (ATP), the main source of energy for cellular metabolism, or transformed into lactate by the enzyme lactate dehydrogenase (LDH). Formed lactate can be either utilized locally or can be released into the bloodstream. With this pathway (Fig. 1) in mind, it is easy to understand why lactate levels can increase during shock or during other critical illness-related physiological stress.

When tissue O_2 needs are no longer covered by O_2 delivery, cell hypoxia occurs. Cell hypoxia in turn inhibits the mitochondrial respiratory chain and modifies the cellular redox potential by making NADH accumulate, thereby inhibiting PDH. This diminishes the amount of pyruvate entering the mitochondria and favours lactate formation from pyruvate. On the other hand, high inflammatory states such as sepsis are accompanied by a vast array of cytokine or hormone-induced mechanisms that accelerate the cellular glycolytic flux [1]. This accelerated glycolysis necessarily leads to over production of lactate, while the cytosolic lactate/pyruvate ratio remains unchanged until the mitochondrial metabolism is saturated by a too high demand or inhibited by hypoxia. The former pathway has long been the only mechanism put forward to explain hyperlactataemia in shock states. In the recent decades, evidence has accumulated showing that the latter, the accelerated glycolysis, was by far the predominant mechanism, particularly in sepsis, to the point that some argue that cell hypoxia has nothing to do with hyperlactataemia observed during shock states [2].

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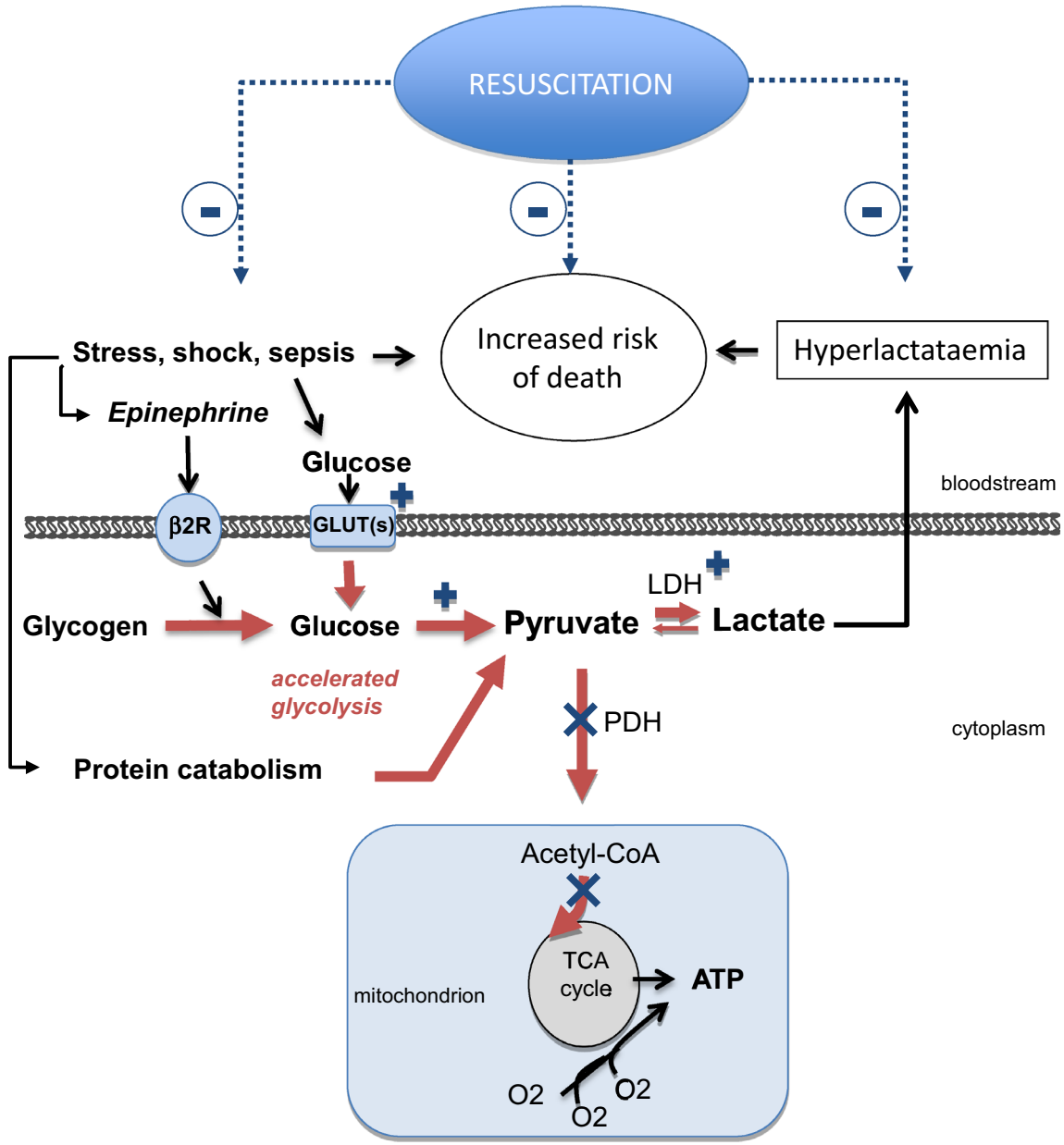

Fig. 1 Sources of blood lactate during shock. *Red arrows* represent the stress-induced accelerated glycolytic flux which results in high energy production (until the TCA and the mitochondrial respiratory chain are saturated) and high lactate production. *Blue plus signs* and *crosses* represent the pathways stimulated or inhibited by hypoxia-induced genomic activity, respectively. *Blue dashed lines* and *minus signs* indicate the expected, parallel, lowering effects of resuscitation on stress, shock, blood lactate level and mortality. *β2R* β2-Adrenergic receptors, *GLUT(s)* glucose transporters, *LDH* lactate dehydrogenase, *PHD* pyruvate dehydrogenase, *TCA* tricarboxylic acid

However, these two pathways can undoubtedly coexist [3]. Notably, hypoxia also enhances glycolysis through hypoxia-inducible factor (HIF-1α) that favours overexpression of genes encoding glucose transporters, glycolytic enzymes, PDH kinase 1 that inhibits PDH, and LDH, all of these resulting in lactate overproduction.

Elevated lactate levels in shock: predictor of adverse outcome

Because serum lactate is a biomarker of tissue hypoperfusion, it is reasonable to assume that its elevation should be associated with poor clinical outcomes. Elevated

serum lactate was observed to be associated with increased risk of short-term death in sepsis and beyond in unselected critically ill patients [4]. In an analysis of a large clinical database by using fractional polynomials, a monotone increasing relationship between lactate and death probability was identified [4]. When lactate levels were categorized into low, intermediate and high subgroups, the in-hospital mortality rates in emergency patients with infection were 15, 25 and 38 %, respectively. Such a dose–response phenomenon confirmed the causal relationship between elevated serum levels and mortality outcome [5]. Likewise, a positive linear relationship was found between lactate and acute-phase death (≤3 days); an initial phase lactate >4 mmol/L was associated with sixfold increase in short-term death. Lactate elevation was also linked to an increased risk of death in a recent analysis of the Surviving Sepsis Campaign database where elevated lactate of more than 4 mmol/L was independently associated with mortality [6]. Although this association was also given in the absence of arterial hypotension (so-called cryptic shock), the combination of hyperlactataemia and arterial hypotension showed the strongest correlation with mortality. Thus, elevated lactate levels represent an alert situation in patients with shock. The authors concluded that a cutoff value of 4 mmol/L was reasonable to initiate aggressive resuscitation [6].

Achieving early lactate clearance in shock: predictor of survival

If resuscitation is successful in restoring tissue oxygenation, it would be expected that elevated lactate concentration starts to decrease. Early septic shock patients with low central venous oxygen saturation ($ScvO_2$) and hyperlactataemia often show rapid return of $ScvO_2$ and lactate returns to normal values when initial resuscitation succeeds in correcting the initial O_2 demand/delivery mismatch [7]. Lactate clearance is defined as the reduction of lactate levels over time (mostly 2–6 h). Indeed, a recent meta-analysis showed that a sustained elevation in lactate is associated with a high risk of death while a high lactate clearance is a strong predictor of survival with a pooled risk ratio (RR) of 0.38 [8]. Early lactate clearance-guided therapy in patients with sepsis has been prospectively investigated in four randomized controlled trials. A meta-analysis of these studies showed that compared to the control group, early lactate clearance-guided control was associated with a reduction in mortality (RR = 0.65) [9]. However, only 286 patients have received this intervention in studies so far and the quality of the data do not yet allow for conclusive evidence.

In conclusion, lactate metabolism is complex in critically ill patients but tissue hypoxia has a significant contribution to hyperlactataemia which is an independent predictor of death in these patients. However, lactate overproduction per se is not the culprit. It makes no sense in only trying to decrease lactate levels, and in fact we have no means to directly modify an increased lactate synthesis. It is also questionable whether a single biomarker alone can or should guide haemodynamic resuscitation; protocolized haemodynamic resuscitation in patients with septic shock was not superior to usual care [10]. In addition to clinical judgement, lactate should rather trigger the search for potential causes of poor tissue oxygenation accessible to therapeutic manipulation. Then, lactate clearance serves as a dynamic biomarker indicating that resuscitation strategies actually are going in the right direction. In the frame of these considerations, measuring lactate levels saves lives in critically ill patients.

Compliance with ethical standards

Conflicts of interest The authors declare that they have no conflict of interest.

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EDITORIAL

Lactate-guided resuscitation saves lives: no

Xavier Monnet[1*], Anthony Delaney[2] and Amber Barnato[3]

"For every complex problem, there is an answer that is clear, simple, and wrong".

H.L. Mencken.

Given the competing priorities in the resuscitation of critically ill patients, it is understandable that clinicians would look to simple measures to guide their resuscitation, and lactate clearance has certainly all the hallmarks of such a simple measure. It has been recently postulated as a marker of the adequacy of resuscitation in critically ill patients [1], particularly those with severe sepsis [2]. Nevertheless, the evidence to support the use of lactate clearance to guide resuscitation is still lacking.

The theoretical basis for using lactate to guide resuscitation during shock states is based upon the false premise that hyperlactatemia specifically indicates tissue hypoxia [3]. While the interruption of aerobic glycolysis inevitably leads to increased formation of lactate, there are many reasons why lactate could increase under aerobic conditions (Table 1) [3, 4]. This in part explains why the major trials of lactate-guided therapy have not shown a consistent clinical benefit.

Two relatively recent randomised clinical trials have used protocols based on lactate clearance. In 348 participants with a blood lactate level of ≥3.0 mEq/L [5], Jansen and colleagues compared two algorithms for haemodynamic management, one of which targeted a fall in the lactate level of ≥20 % every 2 h. In the lactate-guided therapy group, the volume of fluid administered over the initial 8 h was slightly but significantly larger and more patients received a vasodilator. There were no differences in lactate levels over the 72-h observation period. There was no significant difference in the unadjusted in-hospital or 28-day mortality rate, even though hospital mortality was reduced when adjusted for risk factors [5].

In the second trial, Jones and colleagues randomised 300 participants with severe sepsis to receive haemodynamic resuscitation based on lactate or central venous oxygen saturation ($ScvO_2$) levels [6]. There were no significant differences in the treatments received by participants in both groups and once again no difference in mortality. Besides these trials, it is also notable that a randomised clinical trial comparing the use of adrenaline to noradrenaline in critically ill patients demonstrated a significant increase in lactate levels, without any differences in clinical outcomes [7]. This provides further evidence that resuscitation guided by changes in lactate levels is very unlikely to improve mortality.

Three reasons may explain why guiding resuscitation of shock states with lactate clearance did not change outcomes in these studies. The first is that lactate is only an imperfect marker of anaerobic metabolism. Many false positives unfortunately arise when using lactate as a marker of tissue hypoxia; therefore using lactate alone to guide haemodynamic resuscitation is in essence limited. Rather than with lactate alone, tissue hypoxia should be assessed in a combined analysis including other indices, such as ScvO2 or indices derived from the venoarterial carbon dioxide pressure gradient [8].

Second, lactate is only a marker of shock severity. So, although the decrease of lactate should be considered a marker for treatment efficacy, lactate clearance should not be the only goal to pursue. As evidenced by the analogy with oliguria in acute kidney injury, oliguria only reflects the severity of the underlying disease and it has become clear that therapy to alter its course, specifically with diuretics, is not only unlikely to change the course of the disease but also potentially harmful [9]. Similarly, it is

*Correspondence: xavier.monnet@bct.aphp.fr
[1] Medical Intensive Care Unit, Inserm UMR S_999, Hôpitaux universitaires Paris-Sud, Université Paris-Sud, Le Kremllin-Bicêtre, France
Full list of author information is available at the end of the article

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Table 1 Sources for lactate production under aerobic conditions

Increased aerobic glycolysis
Increased activity of the Na+/K+ ATPase
Liver failure
Decrease in lactate clearance
Renal failure
Decrease in lactate clearance
Mitochondrial dysfunction
Impairment of mitochondrial function during sepsis, mainly related to nitric oxide and peroxynitrites
Lung injury
Metabolic adaptation to inflammatory mediators
Alkalosis
Stimulation of the phosphofructokinase enzyme
Drugs and toxics
Nucleoside reverse transcriptase inhibitors, metformine, cyanide and methanol intoxication

quite probable that the degree of hyperlactatemia reflects the severity of the underlying insult and that therapy to alter lactate levels is potentially harmful rather than beneficial.

Third, lactate is a diagnostic tool and it is unrealistic to expect that medical strategies could alter prognosis differently if the only difference is one diagnostic tool and not therapeutic options. In this regard, lactate clearance has the same limitations as the pulmonary artery catheter. The most rational reason why the latter has never demonstrated any clinical benefit [10] is that in the studies investigating its influence on outcomes, no protocolized treatment was ever attached to its use.

While it remains the Holy Grail of critical care medicine to identify a tool that can improve the resuscitation of acutely unwell patients, this remains elusive. Given the complex physiology and pathophysiology of lactate metabolism and the lack of evidence from randomised clinical trials to show a benefit of lactate-guided therapy, one can only conclude that there is no reason to believe that lactate-guided resuscitation saves lives.

Author details
[1] Medical Intensive Care Unit, Inserm UMR S_999, Hôpitaux universitaires Paris-Sud, Université Paris-Sud, Le Kremllin-Bicêtre, France. [2] Northern Clinical School, Sydney Medical School, University of Sydney, Sydney, New South Wales, Australia. [3] Section of Decision Sciences, Division of General Internal Medicine, Department of Medicine, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania, USA.

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EDITORIAL

Lactate-guided resuscitation saves lives: we are not sure

Jan Bakker[1,2,3*], Daniel de Backer[4,5] and Glenn Hernandez[2]

A fundamental objective of septic shock resuscitation is rapid restoration of tissue perfusion. However, one of the most crucial unresolved challenges is to identify a clinical physiological variable that closely reflects global or regional hypoperfusion, or cellular hypoxia, and thus could be potentially used as an accurate resuscitation target.

Since the first description of lactate levels in humans, hyperlactatemia has been traditionally considered as a signal of tissue hypoxia. Both experimental and clinical studies have shown that a reduction in global oxygen delivery will ultimately result in a decrease in oxygen consumption. When oxygen demand remains stable, this decrease in oxygen consumption hallmarks the occurrence of tissue hypoxia and is associated with a sharp increase in lactate levels [1, 2].

However as lactate is a normal product of glucose metabolism, many other factors could increase lactate levels even in the presence of adequate oxygen supply. Probably the most confounding factor is adrenergic-driven aerobic glycolysis triggered by stress situations. Circulatory failure is associated with significant sympathetic activation resulting in increased muscle release of lactate as a systemic metabolic fuel [3]. Thus, persistent hyperlactatemia could simply be a marker of the severity of shock or stress rather than reflecting real impairment of tissue perfusion/oxygenation.

Other factors, particularly abnormal lactate clearance, may also contribute to hyperlactatemia in the presence of adequate perfusion, although the evidence is not uniform. Whereas Levraut et al. [4] demonstrated that impaired clearance was a significant cause of mild hyperlactatemia in stable septic patients, Revelly et al. [5] demonstrated, with stable isotopes, that lactate clearance was not the main cause of hyperlactatemia. More recently, Tapia et al. [6] showed an almost negligible exogenous lactate clearance in early experimental septic shock despite preserved liver perfusion and a concomitant normal clearance of the alcohol sugar sorbitol.

In summary, persistent hyperlactatemia may represent a state of physiological disequilibrium between increased production (either aerobic or anaerobic) and impaired clearance. In this sense, pursuing lactate normalization through further resuscitation with fluids or inotropes when other signs of tissue hypoperfusion have disappeared may expose the patient to the toxicity of over-resuscitation without any clear benefit. This highlights one of the major dilemmas during shock resuscitation: when to consider that a persistent hyperlactatemia is still the consequence of inadequate perfusion. A couple of algorithms to address this question have been proposed and are based on multimodal perfusion monitoring. Persistent hyperlactatemia but with normal central venous oxygen saturation ($ScvO_2$), central venous-arterial pCO_2 gradient [$P(cv\text{-}a)CO_2$], and peripheral perfusion may indicate a lower probability of residual hypoperfusion, although this needs to be confirmed by future studies.

In support of this idea, a recent study [7] suggested that the time course of lactate normalization during a successful resuscitation follows a biphasic curve: an early rapid response (a flow-responsive phase) followed by a later slower recovery trend potentially explained by non-flow-dependent mechanisms (Fig. 1). Interestingly, some flow-responsive variables such as $ScvO_2$, $P(cv\text{-}a)CO_2$, and capillary refill time (CRT) exhibited much higher normalization rates at 6 h than lactate. Only half of this cohort of survivors normalized lactate at 24 h.

*Correspondence: jan.bakker@erasmusmc.nl
[1] Department Intensive Care Adults, Erasmus MC University Medical Center, Room H625, P.O. Box 2040, 3000 CA Rotterdam, The Netherlands
Full list of author information is available at the end of the article

Contrasting viewpoints can be found at: doi:10.1007/s00134-015-4196-0 and doi:10.1007/s00134-016-4235-5.

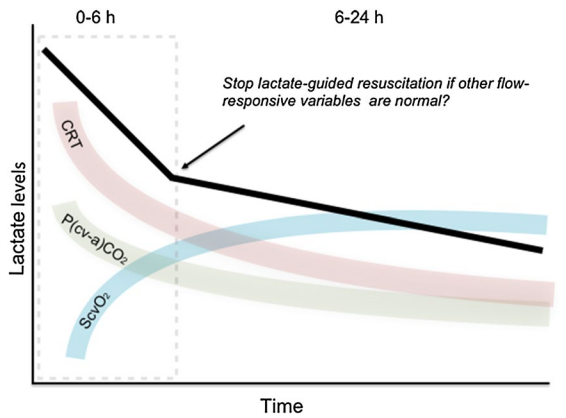

Fig. 1 Theoretical recovery time-course of hyperlactatemia in septic shock survivors shows a biphasic curve with an early rapid decrease associated with normalization of other flow-responsive variables, and a much slower recovery trend after this initial phase, a fact potentially explained by non-flow-dependent mechanisms (adapted from [7]). *CRT* capillary refill time, $P(cv\text{-}a)CO_2$ central venous to arterial pCO_2 gradient, $ScvO_2$ central venous O_2 saturation

Admittedly, other series found slower normalization of some of these variables, which highlights the interest of multimodal monitoring.

Some data tend to support that lactate-guided resuscitation strategies should be associated with multimodal perfusion monitoring and be focused on the early phase. De Backer et al. demonstrated that early improvement of microcirculatory flow with dobutamine was associated with rapid decrease in lactate [8]. A recently published therapeutic algorithm focused on lactate-driven resuscitation exclusively in the first 8 h of ICU management with a significant favorable impact on outcome [9]. A recent meta-analysis also showed that early resuscitation was associated with improved outcome, whereas late treatment was not [10].

To add to the complexity, an important finding in the study by Jansen et al. [9] was that the time course of lactate levels was identical in both the protocol and control group, although the treatment team had no access to lactate levels in the control group. The differences in hemodynamic management between the two groups were minor although in agreement with the pivotal study on early goal-directed therapy: more intensive treatment in the study period and less in the follow-up period for the protocol patients when compared to the control group patients. Although the survival was significantly better in the protocol group this was not reflected by the changes in lactate levels, either in the study period (first 8 h) or in the follow-up period (up to 72 h following inclusion). In addition, van Genderen et al. [11] recently showed that limiting fluid resuscitation in patients with a persistent clinical problem (increased lactate levels, low urine output, persisting hypotension, etc.) but with normal peripheral perfusion was safe and associated with an improvement in organ function. These findings raise some doubts over the whole conception of lactate-guided resuscitation.

Consequently a general recommendation to target the circulation in patients with increased lactate levels is too simplistic and not sufficiently supported by clinical studies. It seems reasonable to optimize systemic hemodynamics and microcirculation early in the phase of septic shock when there is a clinical problem and markers of microcirculatory perfusion are abnormal. In this phase several flow-responsive variables will probably improve in parallel. After this initial resuscitation, persistently elevated lactate levels probably reflect an ongoing septic process, hyperadrenergia, or metabolic deterioration, especially if the other perfusion variables are normal.

In the meantime, whenever lactate levels rise in a septic patient, the patient is at increased risk of morbidity and mortality. This first requires a thorough investigation into the likely causes of this hyperlactatemia. When abnormal tissue perfusion or oxygenation is likely involved, optimizing global hemodynamics and microcirculation for a short period of time is associated with improved outcome.

Author details
[1] Department Intensive Care Adults, Erasmus MC University Medical Center, Room H625, P.O. Box 2040, 3000 CA Rotterdam, The Netherlands. [2] Departamento de Medicina Intensiva, Facultad de Medicina, Pontificia Universidad Católica de Chile, Santiago, Chile. [3] Division of Pulmonary, Allergy, and Critical Care Medicine, Department of Medicine, Columbia University Medical Center, New York, USA. [4] Université Libre de Bruxelles, Brussels, Belgium. [5] Department of Intensive Care, CHIREC Hospitals, Brussels, Belgium.

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